PATENT
Attorney Docket No. VACCINE-07083

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: David R. Millich *et al.*
Serial No.: 10/630,070
Filed: 07/30/2003
Entitled: **Rodent Hepatitis B Virus Core Proteins As Vaccine Platforms And Methods Of Use Thereof**

Group No.: 1648
Examiner: Salvoza, M.F.C.

DECLARATION UNDER 37 C.F.R. § 1.132

ORIGINAL

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTED BY FACSIMILE
CAL 2/20/07

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)(a)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: 2/20/2007 By: Christy A. Lebutt

Dear Sir or Madam:

I, DARRELL L. PETERSON, hereby declare and state, under penalty of perjury, that:
(name)

1. I am an individual having expertise in producing hepadnavirus core particles as epitope carriers. I am the subject of the attached Curriculum Vitae (Tab 1) and author of the publications shown on the list attached thereto. On the basis of the information and facts contained in these documents, I submit that I am qualified to speak on the level of ordinary skill in the art of the claimed invention.

2. I am familiar with the Office Action dated August 10, 2006 in regard to the above-named patent application and confirm that I have read and understand pending claims.

3. In this Office Action, the Examiner rejected Claims 1-12 and 16-20 as allegedly unpatentable over Pumpens *et al.*, *Intervirology*, 38:63-74, 1995 (Pumpens); and rejected Claim

13 as allegedly being unpatentable over Pumpens, in view of Zlotnick *et al.*, *Proc Natl Acad Sci USA*, 94.9556-9561, 1997 (Zlotnick). The Examiner argues that it:

> would be obvious to one or ordinary skill in the art that SEQ ID NO:38, which matched the published sequence for WHV as published by Galibert [*et al.*, *Virology*, 41:51-65, 1982] to use the core molecule as an epitope carrier as described by Pumpens because of the strong similarity of WHC core antigen to the human counterpart.
>
> One of ordinary skill in the art would have expected to achieve a hepatitis B virus core antigen sequence as an epitope carrier based on the WHV sequences because the techniques involved were well developed at the time of applicant's invention (Office Action, page 6).

4. In contrast to the Examiner's conclusion, one of skill in the art at the time the application was filed would not be motivated to substitute woodchuck hepadna virus core antigens (WHcAg) for human hepatitis B virus core antigens (HBcAg) for the purpose of producing an epitope carrier on the basis of the modest structural conservation between these structures as taught by Pumpens. In addition, one of skill in the art would not possess a reasonable expectation of success in achieving an antigenic composition comprising a WHcAg as an epitope carrier on the basis of a 70% sequence identity between WHcAg and HBcAg. Some reasons that support this contention are discussed below:

Prior to this subject patent application the success rate for insertion of foreign epitopes onto the hepatitis B core (HBcAg) and assembly into hybrid-HBcAg particles was less than 50% as acknowledged by all practitioners of this technology including Birken, Pumpens ,Zlotnick and myself. The inventors of the technology described in this patent application have increased the success rate to over 90% by using rodent hepadnavirus core proteins including the woodchuck core (WHcAg). Specifically, Birkett lists a large number of epitopes which he failed to insert and which did not allow assembly of hybrid-HBcAg particles using the HBcAg as a platform (Table 7 of US Patent applications 09/931,325 ; 09/930,915 and PCT 01/25625). In contrast, the inventors of the technology described in this application were successful in inserting 3 of 3 exemplary epitopes that were on the list of failures of Birkett using the WHcAg platform (Paragraph [0306] and Table 8).If use of the WHcAg as a vaccine platform was an obvious way of circumventing the severe assembly problems inherent in the use of the HBcAg and of raising the success rate from less than 50% to over 90%, why didn't Birken, Pumpens, Zlotnick or other practitioners at the time attempt to use the WHcAg during the nearly 20 years of experimentation with the HBcAg ? To my knowledge there was no attempt to insert foreign epitopes into the WHcAg prior to the work described in this patent application.

In my opinion the practitioners of the HBcAg technology did not even try using the WHcAg because the ability of the WHcAg to tolerate insertions of foreign epitopes and the immunologic data regarding the enhanced immunogenicity, non-crossreactivity and general superiority of the

WHcAg were not known at the time. In fact, the only reference by the HBcAg practitioners to the WHcAg in papers and patent applications was a general and mistaken statement regarding the " similarity" of the WHcAg to the HBcAg. This assumption of " similarity " was not based on any experimental evidence. In fact, even the evidence at the time did not suggest "similarity " given the 33% amino acid difference between WHcAg and HBcAg and given the fact that the WHcAg is derived from a non-human pathogen unlike the HBcAg. The inventors of the technology described in this patent application demonstrated for the first time and experimentally that the WHcAg is NOT similar to the HBcAg in terms of its immunologic properties (ie., enhanced immunogenicity, non-crossreactivity to HBcAg at the T cell and B cell levels) and in terms of its superior
function as a vaccine carrier platform (ie., over 90% success rate versus the less than 50% success rate using the HBcAg).

The basic scientific information relevant to the use of the WHcAg as a vaccine platform was unknown prior to this application and similarly the advantages could not have been known, therefore, no expectation of success was present prior to this application and it was therefore not obvious to use the WHcAg as a vaccine platform. The best proof of this principle is the fact that prior to this application no attempt had been made to use the WHcAg or other rodent hepadnavirus core proteins as vaccine platforms.

5. I further declare that all statements made herein are of my own knowledge, are true, and that all statements are made on information and belief that are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application of any patent issued thereon.

Dated: 13 Feb 2007 By: Darrell E Peterson

Signature

Darrell Peterson

Name

PATENT
Attorney Docket No. **VACCINE-07083**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: David R. Milich *et al.*
Serial No.: 10/630,070 Group No.: 1648
Filed: 07/30/2003 Examiner: Salvoza, M.F.G.
Entitled: **Rodent Hepatitis B Virus Core Proteins As Vaccine Platforms And Methods Of Use Thereof**

DECLARATION UNDER 37 C.F.R. § 1.132

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: _____ By: _____

Dear Sir or Madam:

I, _____, hereby declare and state, under penalty of perjury, that: (name)

1. I am an individual having expertise in producing hepadna virus core particles as epitope carriers. I am the subject of the attached Curriculum Vitae (Tab 1) and author of the publications shown on the list attached thereto. On the basis of the information and facts contained in these documents, I submit that I am qualified to speak on the level of ordinary skill in the art of the claimed invention.

2. I am familiar with the Office Action dated August 10, 2006 in regard to the above-named patent application and confirm that I have read and understand pending claims.

3. In this Office Action, the Examiner rejected Claims 1-12 and 16-20 as allegedly unpatentable over Pumpens *et al., Intervirology,* 38:63-74, 1995 (Pumpens); and rejected Claim

13 as allegedly being unpatentable over Pumpens, in view of Zlotnick *et al., Proc Natl Acad Sci USA*, 94:9556-9561, 1997 (Zlotnick). The Examiner argues that it:

> would be obvious to one or ordinary skill in the art that SEQ ID NO:38, which matched the published sequence for WHV as published by Galibert [*et al., Virology,* 41:51-65, 1982] to use the core molecule as an epitope carrier as described by Pumpens because of the strong similarity of WHC core antigen to the human counterpart.
>
> One of ordinary skill in the art would have expected to achieve a hepatitis B virus core antigen sequence as an epitope carrier based on the WHV sequences because the techniques involved were well developed at the time of applicant's invention (Office Action, page 6).

4. In contrast to the Examiner's conclusion, one of skill in the art at the time the application was filed would not be motivated to substitute woodchuck hepadna virus core antigens (WHcAg) for human hepatitis B virus core antigens (HBcAg) for the purpose of producing an epitope carrier on the basis of the modest structural conservation between these structures as taught by Pumpens. In addition, one of skill in the art would not possess a reasonable expectation of success in achieving an antigenic composition comprising a WHcAg as an epitope carrier on the basis of a 70% sequence identity between WHcAg and HBcAg. Some reasons that support this contention are discussed below.

Prior to this subject patent application the success rate for insertion of foreign epitopes onto the hepatitis B core (HBcAg) and assembly into hybrid-HBcAg particles was less than 50% as acknowledged by all practitioners of this technology including Birkett, Pumpens, Zlotnick and myself. The inventors of the technology described in this patent application have increased the success rate to over 90% by using rodent hepadnavirus core proteins including the woodchuck core (WHcAg). Specifically, Birkett lists a large number of epitopes which he failed to insert and which did not allow assembly of hybrid-HBcAg particles using the HBcAg as a platform (Table 7 of US Patent applications 09/931,325, 09/930,915 and PCT 01/25625). In contrast, the inventors of the technology described in this application were successful in inserting 3 of 3 exemplary epitopes that were on the list of failures of Birkett using the WHcAg platform (Paragraph [0306] and Table 8). If use of the WHcAg as a vaccine platform was an obvious way of circumventing the severe assembly problems inherent in the use of the HBcAg and of raising the success rate from less than 50% to over 90%, why didn't Birkett, Pumpens, Zlotnick or other practitioners at the time attempt to use the WHcAg during the nearly 20 years of experimentation with the HBcAg? T o my knowledge there was no attempt to insert foreign epitopes into the WHcAg prior to the work described in this patent application.

In my opinion the practitioners of the HBcAg technology did not even try using the WHcAg because the ability of the WHcAg to tolerate insertions of foreign epitopes and the immunologic data regarding the enhanced immunogenicity, non-crossreactivity and general superiority of the

WHcAg were not known at the time. In fact, the only reference by the HBcAg practitioners to the WHcAg in papers and patent applications was a general and mistaken statement regarding the "similarity" of the WHcAg to the HBcAg. This assumption of "similarity" was not based on any experimental evidence. In fact, even the evidence at the time did not suggest "similarity" given the 33% amino acid difference between WHcAg and HBcAg and given the fact that the technology described in this patent application demonstrated for the first time and experimentally that the WHcAg is NOT similar to the HBcAg in terms of its immunology properties (ie., enhanced immunogenicity, non-crossreactivity to HBcAg at the T and B cell levels) and in terms of its superior
function as a vaccine carrier platform (ie., over 90% success rate versus the less than 50% success rate using the HBcAg).

The basic scientific information relevant to the use of the WHcAg as a vaccine platform was unknown prior to this application and similarly the advantages could not have been known, therefore, no expectation of success was present prior to this application and it was therefore not obvious to use the WHcAg as a vaccine platform. The best proof of this principle is the fact that prior to this application no attempt had been made to use the WHcAg or other rodent hepadnavirus core proteins as vaccine platforms.

5. I further declare that all statements made herein are of my own knowledge, are true, and that all statements are made on information and belief that are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application of any patent issued thereon.

Dated: _____ By: _____
Signature

_____
Name